REMARKS

Claims 1, 6, 12, 13, 27, 36, 46, 52, 53, 60, and 97-102 are pending. In this amendment, claims 1, 6, 12, 13, 27, 36, 46, 52, 53, 60, and 97-102 (all currently pending claims) are canceled and new claims 103-132 are presented.

Claims 103-132 are reformulation of previously pending claims and are supported by previous claims and the specification. New claims 108, 114, 123 and 132 are supported by, *inter alia,* p. 14 lines 19-21 of the specification. New claims 116 and 125 are supported by, *inter alia,* p. 4, lines 4-10 of the specification.

Interview Summary

New claims 103-132 are presented in accordance with the Examiner Interview held on October 26, 2010.

In the Examiner Interview, there was a discussion on the 35 U.S.C. § 112, second paragraph issues. There was further discussion on the differences between the prior art of record and the invention. Dr. Hoon indicated that the loss of heterozygosity of the claimed serum markers was found in type III and type IV melanoma. The examiner noted that the broadest claim does not require any clinical indication. The examiner suggested that the amendment of the claims to be directed to increased likelihood of type III or type IV melanoma in conjunction with a declaration of Dr. Hoon presenting data and details presented would require reconsideration of the obviousness type rejections. No agreement on patentabiity was reached .

Rejections under 35 U.S.C. § 103(a)

In the Office Action, claims 1, 6, 12, 13, 27 36, 46, 52, 53, 60 and 97-102 are

rejected under 35 U.S.C. § 103(a) as being unpatentable over Soengas, et al. (Nature, 2001, volume 409, pages 207-211) in view of Gocke et al. (US Patent 6156504). Although those claims have been canceled, new claims 103-132 are a reformulation of the prior claims and the obviousness rejection is consequently addressed below.

The premise of the rejection is that "it would have been prima facie obvious to one of ordinary skill in the art at the time the inventions was made to improve the Soengas method of detecting the presence of markers D12S1657, D12S393, D12S1706 and D12S346 by amplification of acellular DNA and comparing to a control sample by use of peripheral blood, plasma, or serum as taught by Gocke, because Gocke teaches blood, plasma, or serum is easily accessible and amenable for DNA amplification and thus detection of nucleic acids." Office Action, p. 5. Applicants respectfully disagree.

As the Office Action notes, "Soengas does not teach the use of acellular DNA from plasma, serum, or blood as a sample." Office Action, p. 4. Gocke does not teach a method of detecting the presence of markers D12S1657, D12S393, D12S1706 and D12S346. Neither Gocke, Soengas, nor the combination of the two teach or suggest methods of predicting the probability of survival, the prognosis, or the efficacy of cancer therapy for metastatic melanoma patients by detecting the loss of heterozygosity at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346.

New claims 103-132 are directed to methods of predicting the probability of survival, the prognosis, or the efficacy of cancer therapy for metastatic melanoma patients by detecting the loss of heterozygosity (LOH) at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346. Submitted with this response is the declaration of Dr. Hoon providing evidentiary support to rebut the Office Action's

assertion of prima facie obviousness.

New claims 103-114 are directed to methods of predicting metastatic melanoma survival and prognosis by determining from a blood sample whether LOH has occurred at DNA markers D12S1657, D12S393, D12S1706, and D12S346 in the patient's acellular DNA by comparing the acellular DNA to a control DNA. New claims 115-132 are directed to methods of predicting the efficacy of cancer for a Stage IV melanoma patient or the responsiveness of a Stage IV melanoma patient to cancer therapy by determining from a blood sample whether LOH has occurred at DNA markers D12S1657, D12S393, D12S1706, and D12S346 in the patient's acellular DNA by comparing the acellular DNA to a control DNA. None of these methods are taught or suggested by Soengas, Gocke or the combination of the two.

The focus of Soengas is Apaf-1 expression and LOH, not LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346. The only data disclosed in Soengas directed to LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346 is in Figures 1b & 1c at p. 207 where Soengas discloses the LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346 in metastatic melanoma tumors and associates the LOH with Apaf-1 expression as determined by measuring mRNA. Hoon Decl. ¶ 4. That is all Soengas discloses with respect to LOH at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346.

Soengas does not teach or direct one of ordinary skill in the art to measure the LOH at microsatellite DNA markers D12S327, D12S1657, D12S393, D12S1706, and D12S346 from acellular DNA derived from the blood of a metastatic melanoma patient to

predict the probability of survival, prognosis, or cancer therapy efficacy. One of ordinary skill in the art could not reasonably predict or assume that LOH of microsatellite DNA markers in a melanoma metastatic tumor would be the same in the acellular DNA derived from a metastatic melanoma patient's blood because the LOH of microsatellite markers from informative metastatic melanoma tumors and informative acellular DNA from metastatic melanoma patient is not identical or predictable. Hoon Decl. ¶ 5. Furthermore, one of ordinary skill in the art, would not be enabled, let alone expect to predict the probability of survival, the prognosis, or the cancer therapy efficacy based upon the LOH data in Soengas because merely detecting LOH of a microsatellite marker does not predict prognosis, outcome or efficacy of treatment. Hoon Decl. ¶ 6.

Moreover, as previously set forth in the prior response to the Office Action, Gocke provided a method of "preferential" amplification of the mutant DNA over the wildtype but not mutant extracellular DNA by selective digestion of the wildtype but not mutant DNA before and/or during and optionally after DNA amplification so that the mutant DNA is selectively amplified. ("Preferably, digestion of the extracted extracellular nucleic acid with an enzyme, … specifically cleaves wildtype but not mutant DNA in the portion of the sequence between the positions of the oligonucleotide primers used to amplify the DNA. Thus, wildtype DNA in the sample cannot be amplified after restriction enzyme digestion, whereas mutant DNA can be amplified, and is preferentially amplified using the method of the invention … the amplification reaction is performed in the presence of a thermoresistant or thermostable restriction endonuclease, which endonuclease specifically cleaves wildtype (but not mutant) forms of extracellular tumor derived or tumor-associated nucleic acid species and therefore inhibits amplification of said species

in the amplification…" Lines 48-63, column 4.

The present claim recites "comparing DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 in the acellular DNA with the same DNA markers in a control DNA" and "determining from the comparison step if the acellular DNA has a loss of heterozygosity at one or more of the DNA markers." Gocke teaches away from determination of loss of heterozygosity by "comparing one or more DNA markers on the acellular DNA with that on a control DNA" because Gocke teaches an ordinary artisan to amplify the mutant, not the wild type DNA. A sample containing acellular DNA that does not show loss of heterozygosity may show loss of heterozygosity if the sample undergoes the Gocke preferential amplification procedure because DNA that has loss of heterozygosity will be preferentially amplified over the DNA that has retained heterozygosity.

Consequently, one of ordinary skill in the art at the time of the invention would not be motivated to combine Soengas in view of Gocke to compare DNA markers in a control DNA with that in acellular DNA from a blood sample, serum sample or plasma sample as claimed to determine loss of heterozygosity of the acellular DNA. Thus, for all the above reasons, new claims 103-132 are patentable over Soengas in view of Gocke.

The other obviousness rejections in the Office Action are a combination of Soengas, Gocke, Taback et al. (Cancer Research (2001) volume 61, pages 5723-5726) Chapman et al. (Journal of Clinical Oncology (1999) volume 17, pages 2745-2751), and also Fujiwara et al. (Cancer Research (1999) volume 59, pages 1567-1571), Healy (Oncogene (1998) volume 16, pages 2213-2218), and O'Day et al. (Journal of Clinical Oncology (1999) volume 17, pages 2752-2761). Office Action, pp. 8, 10, 12 and 16-17.

The arguments set forth in the Office Action essentially state that "Taback teaches loss of heterozygosity or microsatellite markers in stage III and IV melanoma is associated with a decreased probability of survival" (Office Action, p. 8), Fujiwara "teaches naked DNA is released from tumor cells" and that LOH acellular markers are "useful in detecting metastatic melanoma cells and disease progression" (Office Action, pp. 13-14), that Chapman discloses that patients with stage IV melanoma have poor survival (Office Action, pp. 17-18), that Healy discloses "genomic instability may determine the clinical behavior of the melanoma and the ultimate clinical survival" (Office Action, p. 19), and O'Day "teaches '5-day modified concurrent biochemotherapy regimen of decarbazine, vinblastine, cisplatin, decrescendo IL-2, interferon alpha-2b and tamoxifen…'" Office Action, p. 19.

Neither Taback nor Fujiwara teach that the LOH at microsatellite DNA markers D12S327, D12S1657, D12S393, D12S1706, and D12S346 can predict survival, prognosis, or cancer therapy efficacy. Thus, while poor survival stage is associated with IV melanoma according to Chapman and genomic instability according to Healy, stage IV melanoma patients having LOH at microsatellite DNA markers D12S327, D12S1657, D12S393, D12S1706, and D12S346 from acellular DNA derived from their blood had poor survival compared with stage IV melanoma patients lacking LOH at those marker in the blood derived acellular DNA. See '956 Specification, Figure 8. Similarly, while prognosis and efficacy of therapy can be predicted from the LOH at microsatellite DNA markers D12S327, D12S1657, D12S393, D12S1706, and D12S346 in acellular DNA for metastatic melanoma patients, the various recited combinations of Soengas, Gocke, Taback, Chapman, Fujiwara, Healy, and O'Day do not teach let alone suggest the

claimed methods of predicting the probability of survival, the prognosis, or the efficacy of cancer therapy for metastatic melanoma patients by detecting the loss of heterozygosity (LOH) at microsatellite DNA markers D12S1657, D12S393, D12S1706 and D12S346 in acellular DNA from a patient blood sample. Consequently, new claims 103-132 are not obvious and patentable.

Claims 115-132 are directed to methods of predicting the efficacy of cancer for a Stage IV melanoma patient or the responsiveness of a Stage IV melanoma patient to cancer therapy by detecting acellular DNA LOH. Claims 115-132 provide a significant clinical advantage over LOH detection using tumor tissue because the method is non-invasive. This methodology provides a particularly significant advantage to Stage IV patients as they often have inoperable tumors (e.g. brain tumors) that pose significant risk for biopsy.

CONCLUSION

In view of the foregoing, it is submitted that the claims are in condition for allowance. A Notice of Allowance is requested. If the Examiner has any questions or believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to contact the undersigned at 310-788-9900.

Respectfully submitted,

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